



Burden of HCV in Bangladesh: Warrants the Screening for Blood Donors



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Abstract

Globally, the morbidity and mortality attributable to hepatitis C virus (HCV) infection continues to increase. Approximately 7,00,000 persons die each year from HCV related complications, which include cirrhosis, hepatocellular carcinoma (HCC) and liver failure. It is estimated about 180 million people having hepatitis C virus infection but most are unaware of their infection. Highest number of transmission of HCV through untested or improperly screened blood transfusion (BT). In every case of BT in Bangladesh, so called proper donor screening done every day. But After reviewing lots of national & international guidelines and papers of blood transfusion, proved that blood donor screening tests and method of testing are not adequate & inappropriate. Lots of multi-transfused thalassemic and hemophiliac patients getting hepatitis C virus undoubtedly. Transfusions should be planned judiciously and side by side, efforts should be made to minimize the risk of transfusion transmissible infections (TTI) through adopting the international guidelines for safe blood transfusion. Awareness and knowledge would be the key to prevent the transfusion of transmissible diseases. Implementations of strict donor selection criteria and use of sensitive laboratory screening tests reduces the incidence of HCV transfusion.

Keywords: Blood transfusion; Blood donor screening; Transfusion transmissible infections

Introduction

Transfusion of blood components (TBC) continues to be an important therapeutic resource into the 21st century [1]. It is a specialized modality of patient management saves million of lives but many patients requiring transfusion do not have timely access to safe blood [2]. The safety of the transfusion lies not only in the correct selection, preparation and administration of blood products, but also in the ability to correctly interpret when such intervention is appropriate [1]. Providing safe and adequate blood should be an integral part of every country's national health care policy and infrastructure [2].

The microbiological safety of blood donations may be affected by donor's exposure to HIV, hepatitis B, hepatitis C, syphilis and

other transfusion-transmissible infections (TTI). Through unsafe blood transfusion these microbial agents may transmit to the recipient blood and can cause morbidity and mortality [3]. The infectious agents may present in the blood for long periods, sometimes in high titers, stability in blood stored at 4 °C or lower, long incubation period before the appearance of clinical signs, asymptomatic phase or only mild symptoms in the blood donor, hence not identifiable during the blood donor selection process [4].

The primary responsibility of a blood transfusion service (BTS) is to provide a safe, sufficient and timely supply of blood and blood products. In fulfilling this responsibility, the BTS should ensure that the act of blood donation is safe and causes no harm

to the donor [3]. However, in developing countries transmission of infectious agents through blood transfusion are continuing [5]. This is mostly due to inability of the test to detect the disease or the diagnostic window during which an acutely infected blood donor may harbor large amounts of highly infectious viruses without developing symptoms or detectable antigen and antibody concentration or laboratory errors [6].

Hepatitis C virus (HCV) is serious threat for South East Asia [7]. Bangladesh, a developing country of South-East Asia, has a population of 160 million [8]. HCV is emerging as one of the major health problem in Bangladesh [7]. It is encountered sporadically in this country [9]. It is one of the main causes of chronic liver disease, cirrhosis and hepatocellular carcinoma (HCC) worldwide and also in Bangladesh [10,11]. It is imperative to screen and diagnose HCV infection in high risk population specially blood donors so that those at risk of progressive liver disease may benefit from anti-viral therapy and counseling [12]. The introduction of highly sensitive second-generation & third-generation screening assays for HCV antibodies (anti-HCV) everywhere, where as Bangladesh usually practiced rapid strip method which is less sensitive & specific with lots of chance of viral missing [6,13]. This review aims to aware all health care practitioners about present dangerous situation of donor screening and wake up the policy makers regarding safe blood transfusion.

Hepatitis C Virus (HCV)

Hepatitis C virus (HCV) is a hepatotropic RNA virus of the genus Hepacivirus in the Flaviviridae family [14]. It was discovered in 1989, and since been identified as the major cause of transfusion associated non-A, non-B hepatitis [6].

Epidemiology & Burden

The number of deaths per year due to HCV-related diseases continues to increase. According to estimates from the Global Burden of Disease study, the number of deaths due to hepatitis C was 3,33,000 in 1990, 4,99,000 in 2010 and 7,04,000 in 2013. A more recent systematic review estimated that 115 million persons are anti-HCV (antibody to HCV) positive and 80 million have chronic infection. The increase in number of deaths reflects the high incidence of hepatitis C [15]. There is lack of representative population study in Bangladesh regarding prevalence of HCV infection [9]. In the past, it was 2.4% (WHO, 1999) [7]. In a recent study from Mahtab et al. [9] that was 0.88%. HCV poses a huge burden on the health of Bangladeshis, being a leading cause of all forms of chronic liver diseases next only to HBV [16,17]. This is similar to the experience in India [18,19], Pakistan [20] and Nepal [21,22]. HCV also ranks to be a leading cause of HCC in Bangladesh [23] as well as in the region including India [18] and Pakistan [24]. There are also published data from Bangladesh identifying HCV to be the etiological agent in 24.1% of patients with chronic liver diseases [25]. In another study in Bangladesh, anti-HCV was positive in 1.7% in acute viral hepatitis, 5.5% in sub-acute hepatic failure, 6.8% in post transfusion hepatitis, 24.1% of chronic liver disease, 9.6% cases hepatocellular carcinoma [26].

Hepatitis C Virus (HCV) Infection

HCV infection can be cured by antiviral treatment; however, due to the asymptomatic nature of the disease, many infected persons are unaware of their infection and for those who are diagnosed, access to treatment remains poor in many settings Figure 1 [15].

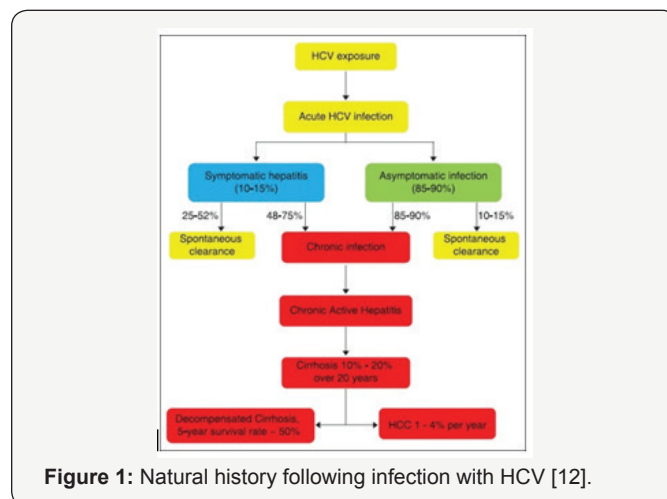


Figure 1: Natural history following infection with HCV [12].

Acute Hepatitis C Virus (HCV) Infection: Most of the cases of acute hepatitis C are asymptomatic (85-90%). Symptomatic acute hepatitis with jaundice is seen in 10-15% cases and asymptomatic infection in 85-90% cases [12]. Diagnosis of acute HCV infection is based on detection of antibodies to HCV (Anti-HCV) by enzyme immunoassay. Presence of anti-HCV indicating history of exposure to HCV but not indicate the resolved infection or chronicity and persist throughout the life [15].

Resolved infection: In 15-45% cases a person clear the HCV within 6 months of exposure without any chronicity. A negative test result for hepatitis C virus RNA in the presence of a positive antibody indicates a resolved infection. The persons who already resolved infection, anti-HCV may persist life-long but are no longer infected with HCV (Figure 2) [15].

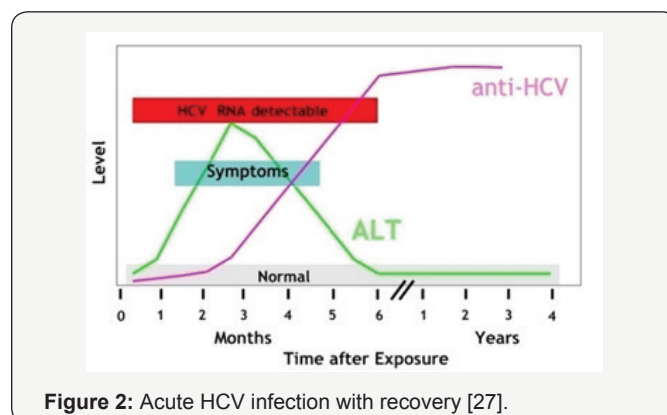


Figure 2: Acute HCV infection with recovery [27].

Chronic Hepatitis C Virus (HCV) infection: Continued presence of HCV RNA in the blood six months or more after acquiring infection is called chronicity. Chronic infection with HCV is usually clinically silent, and is only very rarely associated with

life-threatening disease. Left untreated, chronic HCV infection can cause chronic liver disease (70-80%), cirrhosis (10-20%) and hepatocellular carcinoma (HCC) (1-4%) (Figure 3) [12,15].

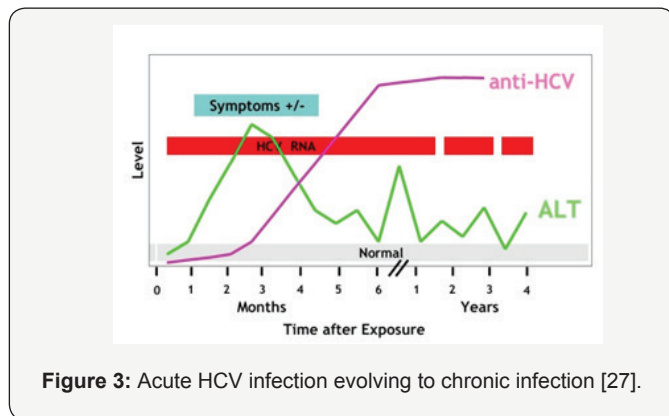


Figure 3: Acute HCV infection evolving to chronic infection [27].

Incubation period

The time between exposure of HCV & appearance of symptoms. It is about 2 weeks to 6 months commonly 6-9 weeks [12,15].

Window Period

This is about 4-6 weeks before developing anti-bodies against HCV. As there is no antibody detection, the ELISA will come up negative [12,15].

Transfusion Transmissible Infections (TTI)

Many viruses [mostly hepatitis B virus, hepatitis C virus, HIV and less commonly cytomegalovirus (CMV) and Epstein Barr Virus (EBV)], bacteria (treponema pallidum) and protozoa (malarial parasite) can be transmitted by transfusion [3,28]. Like other developing countries, blood banking in Bangladesh does not get enough attention for development from authorities. Many blood recipients remained at risk of TTI transmission as a result of poor blood donor recruitment and the use of low-quality testing in TTI screening [29].

Transmission of HCV through transfusion

HCV is spread predominantly by percutaneous or mucosal exposure to infected blood [15]. Several studies from different countries including Bangladesh indicate that, blood transfusion is the main source for transmission of HCV (Table 1 & 2).

Table 1: Seroprevalence of HCV among multi-transfused Thalassemic children.

Country	Year	Total Children	Anti-HCV Positive
India [30]	2017	211	75 (35.5%)
Egypt [31]	2016	97	36 (37.1%)
Iran [32]	2016	90	9 (10.0%)
Pakistan [33]	2015	145	99 (68.2%)
Malaysia [34]	2015	100	18 (18.0%)
Bangladesh [35]	2014	200	4 (2.0%)
Bangladesh [36]	2013	100	31 (31.0%)
India [37]	2013	218	18 (8.25%)
Bangladesh [38]	2007	42	7 (16.7%)
Bangladesh [39]	2003	152	19 (12.5%)

Table 2: Seroprevalence of HCV among multi-transfused Hemophiliac children.

Country	Year	Total Children	Anti-HCV Positive
Pakistan[40]	2017	396	72 (18.0%)
USA [41]	2015	59	39 (66.1%)
Iran [42]	2015	146	13 (8.9%)
Iran [43]	2014	77	44 (49.4%)
Iran [44]	2012	87	47 (54.0%)
Iran [45]	2011	615	495 (80.4%)
Iran [46]	2011	1095	802 (72.3%)
Iran [47]	2007	81	24 (29.6%)
Iran [48]	2002	101	72 (71.3%)
Brazil [49]	2002	90	55 (61.1%)

Donor screening tests for HCV in Bangladesh & Abroad

Nowadays in Bangladesh, routine screening of blood donors for HCV is only anti-HBC (antibody to HCV) [50]. Along this test, International organizations added some recent tests for prevention of HCV transmission. With anti-HCV, American red cross [51], Australian red cross[52], U.S. food & drug administration (FDA) [53], United Kingdom (UK) [54], Singapore health science authority [55], recommends Nucleic acid testing (NAT) [56] (It is a molecular technique for screening of HCV which providing an additional layer of blood safety). Centers for disease control & prevention (CDC) [57] recommends the cost effective approach. If anti-HCV positive then they advice HCV RNA. World Health Organization (WHO) [3] recommends HCV antibody immunoassay or a combination HCV antigen-antibody immunoassay. American association for the study of liver diseases (AASLD) [58] and American family physician (AFP) [59] recommends like CDC. But when history of exposure to HCV or having suspected liver disease or HCV infection should do HCV RNA. European association for the study of liver (EASL) [10] is little bit different. With positive anti-HCV, HCV RNA is recommended. If HCV RNA not possible then HCV core antigen (HCV Ag) is the answer. I think western world doing the great job with no chance of missing HCV.

Limitations of antibody to Hepatitis C Virus (Anti-HCV) test

Anti-HCV usually appear in the blood after 6-10 weeks of infection by enzyme immunoassay. Due to large gap between infection & anti-body appearance, lots of chance of false positive & false negative results.

False Positive results of Anti-HCV [60]

- I. Antibodies that the immune system has produced to combat infections other than hepatitis C (known as “cross-reactive”). The ELISA winds up picking up on these antibodies’ presence and incorrectly coming up positive.
- II. If individuals suffering from autoimmune disorders like lupus.

False Negative results of Anti-HCV [61]

- I. Incubation period (It is about 2 weeks to 6 months commonly 6-9 weeks).
- II. Window period (around 4-6 weeks before developing antibodies against HCV).
- III. Initial period of infection (before appearing antibody).
- IV. If patient is immuno-compromised
- V. Low viremia

Advantages of HCV Core Antigen (HCV Ag)

During the past decade, several assays for the detection of the core antigen of HCV by ELISA (Enzyme immunoassays) or CLIA (Chemiluminescent immunoassays) have been developed. These assays were envisioned as alternatives to NAT to be used in resource-limited settings, where molecular laboratory services are either not available or not widely utilized owing to cost issues. Since these assays are either ELISA or CLIA based, they are user friendly, require less technical expertise and are less expensive compared to molecular techniques [12]. HCV core antigen assays are less sensitive than HCV RNA assays (lower limit of detection equivalent to approximately 500 to 3000 HCV RNAIU/ml) [10]. But it is more sensitive than anti-HCV. It appears just after appearing of HCV RNA (about 7-8 weeks earlier than the anti-HCV) with small window period and it’s follow the HCV RNA dynamics [12].

Advantages of HCV RNA

It is the beautiful test which developed world already adopted. It diagnosed HCV infection in incubation period (after 1 week of infection), window period and with low viremia (as low as 30 copies/ml). Nucleic acid testing (NAT) is considered the ‘gold standard’ for detecting active HCV replication. It is extremely useful in establishing the diagnosis of acute HCV infection, since RNA is detectable as early as 1 week after exposure via needle-stick or blood transfusion, and at least 4-6 weeks prior to seroconversion as demonstrated in a number of transmission settings. The diagnosis of HCV infection is established with antibody screening followed by NAT for HCV RNA (Table 3) [12].

Table 3: Interpretation of donor screening tests regarding HCV [61].

Tests	Results	Interpretation
Anti-HCV HCV RNA	Reactive Detected	Acute or chronic HCV infection
Anti-HCV HCV RNA	Non-reactive Non-detected	Never exposure to HCV
Anti-HCV HCV RNA	Reactive Non-detected	Resolved HCV infection
Anti-HCV HCV RNA	Non-reactive Detected	Early acute HCV infection or chronic HCV infection inimmune compromised person

Tests Methods

According to WHO & National guideline, the main types of assay used for blood screening of HBV are [50]:

- Immunoassays (IAs):
 - Enzyme immunoassays (EIAs)
 - Chemiluminescent immunoassays (CLIAs)
 - Rapid/simple single-use assays (rapid tests)
 - Nucleic acid amplification technology (NAT) assays.
8. Universal Choice

The blood transfusion department of medical colleges, institutes and specialized hospitals should perform EIAs and CLIAs for blood screening in addition to the current system of rapid testing [50].

In Special Situation

Only rapid tests may be considered in case emergency screening (when blood is needed urgently) or in remote areas with low workloads or limited number of tests are performed daily and limited facilities, when equipment is lacking or where there may be no electricity e.g. district blood centers and Upazila health complexes [50].

Why EIAs and CLIAs Rather than Strip

In case of rapid strip test, lots of false positive/negative results may occur. It is most commonly used, only 30 taka/strip, less sensitive & specific, manual entry of test results and not recommended by WHO as a universal screening of blood donors in Bangladesh. When false positive results occur, prospective blood donors are unnecessarily excluded from blood donation. On the other hand, when false negatives occur, this poses a great challenge to the quality and reliability of blood screening and to patient safety. Errors may also be produced if samples for re-testing are improperly stored and/or transported. On the other side, quite unlikely to occur when screening is done by EIA, Chemiluminoassay, or PCR technology [50].

Present Situation in Bangladesh

In Bangladesh, Transfusion Transmissible Infections (TTI) screening is done mainly by rapid assay. Only at private sector centers (Square Hospital Limited [62] & another is Apollo Hospital, Dhaka [63]) are screening done by EIA/ CLIA (Chemiluminescent Assay). The blood donation system in Bangladesh is decentralized; all centers collect, and process and distribute blood. A beautiful study was done in 2013, which was organized by WHO, DGHS (Director General Health Services) & IEDCR (Institute of Epidemiology, Disease Control and Research) to assess the donor screening quality of different blood transfusion centers of Bangladesh. A total of 12 centers from Dhaka city (Apollo hospital, Square hospital, United hospital, Lab Aid hospital, Armed forces

institutes of pathology, Bangladesh Medical College hospital, Cancer and rehabilitation hospital, Chest diseases hospital, Kidney and urology hospital, Institutes of child and maternal health etc) and 15 centers from outside the Dhaka (Rajshahi medical college hospital, Khulna medical college hospital, Faridpur medical college hospital, Comilla medical college hospital & lots of district hospitals) were included in this study. A total 915 blood samples were received from testing centers and all samples were accepted for testing in IEDCR. Out of 27 testing centers, results from 18 centers were correct (66.67%) and those from 9 centers were incorrect (33.33%) when compared with the results obtained at IEDCR. Among incorrect results, HBV (53.3%) is the dominant one followed by HCV (40%) and malaria (6.7%). No results of disparity observed among HIV and syphilis cases [13].

Conclusion

Although so called proper donor screening prior to blood transfusion every time, they were unable to prevent HCV transmission. Lots of national & international studies proved that, multi-transfused thalassemic & hemophiliac patients gradually positive with HCV after few times of blood transfusion. Not only the strip method but also only antibody (anti-HCV) screening may miss the HCV anytime. The risk of disease transmission increases many fold if blood donor selection is inappropriate and method of testing is inadequate. The hazards of blood transfusion, specially the risk of transfusion transmissible infections especially HCV are now the burning issue. The policy makers, academicians, physicians and hepatologists are equally unaware of the seriousness, loop holes and magnitudes of ongoing blood transfusion program of this country. Percentage of anti-HCV negative (with strip method) healthy donors without knowing the HCV RNA status warrants the decision makers for rethinking about silent HCV infection.

Recommendations

- Antibody (anti-HCV) screening should be on Enzyme immunoassays (EIAs) and Chemiluminescent immunoassays (CLIAs) in place of strip method.
- Nucleic acid testing (NAT) for HCV should be included to avoid of missing initial period of infection/window period and for safe blood transfusion in Bangladesh.
- Core antigen (HCV Ag) may include in national donor screening program if nucleic acid testing (NAT) for HCV are not available or not affordable.

Future Prospect

Establishment of a nationally coordinated blood transfusion service, collection of blood only from voluntary donors, testing of all blood for compatibility and transfusion transmissible infections (TTIs) with appropriate method of testing and reduction of unnecessary transfusion will be the key factors for excellent blood transfusion service (BTS) in future.

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